Amendments to the Specification:

Please make the following replacements to the pending application.

At Page 1, line 1 please replace the title with the following amended version of the title:

~~Dystrophin related protein (DROP1)~~ Drop1, a novel marker for carcinomas

At Page 1, please insert the following as paragraph 1:

This application is a National Stage application filed under 35 U.S.C. § 371 and claims priority to International Application No. PCT/EP2004/003538, filed April 2, 2004, which claims priority to European patent application EP03007680.6, filed April 3, 2003.

At Page 1, please insert the following as paragraph 2:

All patents, patent applications and publications cited herein are hereby incorporated by reference in their entireties. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein.

At Page 1, please insert the following as paragraph 3:

A portion of the disclosure of this patent document contains material which is subject to copyright protection. The copyright owner has no objection to the facsimile reproduction by anyone of the patent document or the patent disclosure, as it appears in the Patent and Trademark Office patent file or records, but otherwise reserves all copyright rights whatsoever.

At Page 5, please replace the paragraph beginning on line 22 (Figure 6 legend) with the following amended version of that paragraph:

The figure shows the location in the contig of sequences mentioned in the text (A). The sequence was established starting with the 681 bp of the differential display fragment 31N/GDOC/1 dd (SEQ ID NO:21). Primers L467 (SEQ ID NO: 22) and U285 (SEQ ID NO:23) (their direction inverted in the final ORF) were derived from it and used throughout for quantitative PCR. "RACE walking" experiments were performed, based on a commercial RACE

ovarian library. Of these, 5R9 (SEQ ID NO:10) marks the 5' region of drop1, 3R9 was used to generate the probes for in situ hybridisation, for multitissue Northern blots, and for the cancer profiling array. For validation of these sequences by overlapping PCR, total cDNA from SKOV-3 ovarian carcinoma cells was used as a template (Drop 1A (SEQ ID NO:17), C (SEQ ID NO:18), B (SEQ ID NO:19), D (SEQ ID NO:27)). The same template yielded the clones used in bacterial and mammalian vectors for expression of domains (Drop1 alpha (SEQ ID NO:12), beta (SEQ ID NO:15), gamma (SEQ ID NO:16), epsilon (SEQ ID NO:20), and C-terminal domain (SEQ ID NO:24)). In total, more than 70 clones were aligned. Only upon completion of the Drop1 structure the enaptin sequence became available, of which here the 5`10 000 bp are shown in SEQ ID NO:9 (B). For ease of comparison the exons are designated accordingly. Drop1 is encoded by the 5´region (exons 2 to 58) of the enaptin gene (147 exons). The Drop1 mRNA and protein, however, are entities different from enaptin. Enaptin exons 07 (SEQ ID NO:13) and 12 (SEQ ID NO:14) are not used in Drop1, and enaptin-exon 58 (SEQ ID NO:26) is read differently: for Drop1 it is read beyond the enaptin-exon58-intron transition. It carries the stop codon for the ORF and a long 3´ UTR (SEQ ID NO:28) that includes the unused sequence of enaptin-exon 59 (SEQ ID NO:29).

At Page 7, please replace the paragraph beginning on line 3 (Figure 10 legend) with the following amended version of that paragraph:

The ORF encodes a protein of 3032 amino acid residues as shown in SEQ ID NO:30. Analysis using SMART (Simple Modular Architecture Research Tool) software indicates two calponin homology (CH) domains, an AAA, four coiled coil (CC) motifs and twelve spectrin-like (SPEC) regions, as highlighted in gray in the sequence and indicated in the margin.

At Page 7, please replace the paragraph beginning on line 10 with the following amended version of that paragraph:

The present invention relates to a nucleic acid molecule encoding the human dystrophin-related polypeptide Drop1 or a polypeptide exhibiting a biological property of Drop1, which is: (a) a nucleic acid molecule encoding a Drop1 polypeptide that consists of the amino acid sequence as depicted in Figure 10 and SEQ ID NO:30;

(b) a nucleic acid molecule consisting of the nucleotide sequence as depicted in Figure 6B and SEQ ID NOS:9-29;

(c) a nucleic acid molecule the sequence of which differs from the sequence of a nucleic acid molecule of (a) or (b) due to the degeneracy of the genetic code;

(d) a nucleic acid molecule, which represents a fragment of a nucleic acid molecule specified in (a) to (c); or

(e) a nucleic acid molecule complementary to the nucleic acid molecule specified in (a) to (d).

At Page 7, please replace the paragraph beginning on line 32 with the following amended version of that paragraph:

In a first embodiment, the invention provides a nucleic acid molecule encoding a Drop1 polypeptide that consists of the amino acid sequence as depicted in Figure 10 and SEQ ID NO:30.

At Page 8, please replace the paragraph beginning on line 10 with the following amended version of that paragraph:

The nucleic acid molecules of the present invention also include molecules which differ from the nucleic acid molecules with sequences shown in Figure 6B (SEQ ID NOS:9-29) due to the degeneracy of the genetic code.

At Page 22, please replace the paragraph at lines 1-2 with the following amended version of that paragraph:

(b) a nucleic acid molecule comprising the nucleotide sequence as depicted in Figure 6B (SEQ ID NOS:9-29) ;

At Page 22, please replace the paragraph beginning at line 15 with the following amended version of that paragraph:

The present invention also provides the pharmaceutical or diagnostic use of nucleic acid molecules encoding a polypeptide the amino acid sequence of which shows an identity of at least 80%, in particular an identity of at least 90%, preferably of at least 95%, 96%, 97%, 98% or 99%

to the amino acid sequence of the polypeptide of Figure 10 (SEQ ID NO:30). The amino acid sequences of such polypeptides are characterized by deletion, substitution and/or insertion of amino acid residue(s) compared to the amino acid sequence ~~shwon~~ shown in Fig. 10 (SEQ ID NO:30) or the result of recombination. They can be naturally occurring variations, for example sequences from other organisms, or mutations that ~~eam~~ can either occur naturally or that have been introduced by genetic mutagenesis. In order to identify and isolate such nucleic acid molecules, the molecules of the invention or parts thereof can be used, for example by means of hybridization. As a hybridization probe nucleic acid molecules can be used, for example, that have exactly or basically the nucleic acid sequence as depicted in Fig. 6B (SEQ ID NOS:9-29), or parts of these sequences. The fragments that have been used as hybridization probes can be synthetic fragments that were produced by means of conventional synthetic methods and the sequence of which basically corresponds to the sequence of the Fig. 6B sequence (SEQ ID NOS:9-29).

At Page 33, please replace the paragraph beginning at line 12 with the following amended version of that paragraph:

Differential display was performed using a modification of Liang's and Pardee's method with a self-designed set of arbitrary primers. A strong difference in expression was found in patient 31 with the arbitrary decamer primer 5' ACAAGGCACC 3' (SEQ ID NO:1) (designated DOC), and a decamer anchor primer 5' TTTTTTTTCG 3' (SEQ ID NO:2), resulting in a 680 bp PCR fragment in normal epithelium, which was absent from the pattern derived from the tumor of the same patient. This fragment was eluted from the gel, amplified, cloned into TOPORII, and sequenced.

At Page 34, please replace the paragraph beginning at line 1 with the following amended version of that paragraph:

1 µl cDNA of the 20 µl RT-mixture (corresponding to 0.5 ng of cDNA);
1 µl Drop1 Upper primer (5' CTGGAGAAACGGCTGTCACAAATA 3' (SEQ ID NO:3) corresponding to positions 8255-8278 in exon 53), 20 µM;

1 µl Drop1 Lower primer (Lower primer 5' CCTCTCTACATAGTCATTCCATTGGCTA 3' (SEQ ID NO:4), complementary to positions 8500-8473 in exon 55), 20 µM;

5 µl cDNA-PCR reaction buffer, 10 x;

1 µl dNTP-Mix, 10 mM;

1 µl advantage-cDNA-polymerase mix, 50 x;

40 µl aqua dest.

At Page 39, please replace the paragraph beginning at line 32 with the following amended version of that paragraph:

The 5' region of the ORF, encoding aar 1 - 396 (Drop1) the two calponin homology domains, was amplified using the primers 5'-GTCGACGATGGCAACCTCCAGAGGGGCCTCCCG-3' (SEQ ID NO:5) with a Sal I restriction site as upper primer (U278) and 5'-GGGCCCTGGTGCCCAGAGGTGCAGGAAGAGA-3' (SEQ ID NO:6) with an Apa I restriction site as lower primer (L1492) and a previously sequenced overlap clone (H) on the basis of cDNA from the SKOV-3 cell line as template (annealing at 68 øC, 25 cycles). The PCR product was cloned into pDrive for amplification and sequencing, cut out with Sal I and Apa I, and cloned into pEGFP-C3 (Clontech, GenBank Accession # U57607), behind a GFP-domain. Correct insertion was confirmed by sequencing. 5-10 x 104COS-7 cells/well were grown in DMEM, containing 10% fetal calf serum, 1% L- glutamine and 1% nonesssential amino acids, for 24 h in Lab-Tek chambered cover glasses, transfected with 0,75 - 1.5 _g of DNA/ well mixed with 3 to 6 _l FuGENE 6 (Roche). After 24 h cells were observed under a Zeiss Axiovert S100 TV microscope (excitation at 485 nm, filter 485/20, - emission at 515 nm, filter 530/30, dichroic mirror 505) using a 20x objective and a Plan-Neofluar oil objective with 63x magnification. Fluorescence images were recorded for 100 to 250 msec with 30% gain.

At Page 40, please replace the paragraph beginning at line 23 with the following amended version of that paragraph:

The carboxyterminal spectrin-like domain of Drop1 was selected as an antigen. cDNA encoding that region was obtained using cDNA from CAOV-3 tumor cells as template, 5'-

GATATCATGTATTTAGATGCGGTCCACGAGTTC-3' (SEQ ID NO:7), containing an EcoR V restriction site as an upper primer, and
5'-GTCGACTGGGGACCCTTGATTTAGAGGTTAACTT-3' (SEQ ID NO:8), containing a Sal I restriction site as lower primer. This primer binds to a sequence in the 3' UTR of Drop1, which in the enaptin gene is located in a putative intron. The PCR product (annealing at 64 øC, 45 cycles) was cloned into TopoTA for amplification and sequencing, cut out with EcoR V and Sal I, and cloned into pET32a for expression in E. coli BL21(DE3).

At Page 50, please replace the paragraph beginning at line 9 with the following amended version of that paragraph:

Drop1 encodes a protein of 349 kDa (Figure 10 and SEQ ID NO:30) that is structurally similar to dystrophin. At the N-terminus it features 2 calponin homology domains followed by an ATPase-domain and 12 spectrin-like domains (Figure 7). The homologues of these structures are known to bind other intracellular or transmembrane proteins.

At Page 50, please replace the paragraph beginning at line 31 with the following amended version of that paragraph:

The 5′ fragment, Drop1α, containing the two calponin homology domains of the open reading frame, was cloned into the eukaryotic expression vector pEGFP-C3 (SEQ ID NO:12). Transfected cells show a distinct fluorescence of nuclei (Figure 8), suggesting a nuclear association of the N-terminal region.

At Page 50, please replace the paragraph beginning at line 31 with the following amended version of that paragraph:

A C-terminal recombinant protein fragment, amino acid residues 2827 – 3032 of SEQ ID NO:30, was produced in bacteria, isolated and purified to serve as an antigen for generation of a monoclonal antibody. A clone that recognized the recombinant protein on an immunoblot also identified a high molecular weight band in cell lysates of SKOV-3 and stained nuclei of the same cells (Figure 9). Additional smaller protein bands in the pellet of the cells presumably are Drop1 degradation products.